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Cleaned Equipment Hold Time

Last month's Cleaning Memo covered issues related to the "Dirty Equipment Hold Time" in cleaning validation. This month's Cleaning Memo covers issues related to the "Cleaned Equipment Hold Time" (which will be abbreviated CEHT). CEHT is sometimes called the expiration or expiry period for the cleaned equipment.

Why is the CEHT important for the control of a cleaning process? Essentially the reason is that nothing stays clean forever (no matter how good it's protected in storage). It should be realized that recontamination of the equipment may be an event-related phenomenon; however, as a practical matter one sets an expiration period of a fixed time assuming certain storage conditions. In dealing with possible ways the equipment could be recontaminated, one should consider both endogenous sources (such as growth of microorganisms already within the equipment) as well as exogenous sources (such as entry of external contaminants into the equipment).

Three important issues for the CEHT include (1) the characteristics of the cleaned equipment, (2) the nature of possible recontaminants, and (3) the storage conditions of the equipment. These three factors are interrelated in terms of effects on recontamination of cleaned equipment.

A major issue related to the characteristics of the cleaned equipment is whether the equipment is stored wet or in a manner such that microbial proliferation is a possibility. This is explicitly covered in the FDA's cleaning validation guidance. If the equipment is stored wet for a sufficient time, there is a reasonable probability microbes will readily grow to an unacceptable level, and thereby render the equipment unsuitable for manufacturing use. Another issue related to the characteristics of the equipment involves possible routes of entry for external contaminants. For small pieces of equipment (scoops, for example) this involves exposure of the item itself. For larger pieces of equipment (tanks, for example) this involves any opening in the equipment.

For possible recontaminants, the two major sources are microbes that may already be in the cleaned equipment and external "dust" which is in the storage atmosphere. Residues such as product residue and cleaning agent residue, which are in the equipment at trace levels, are generally not expected to change over time. The only exception to this may involve an active, which is present in the cleaned equipment at an acceptable level at the end of the cleaning process, but which over times degrades to form a specie that (because of unusual toxicity/ safety concerns) would make the equipment unacceptable for use. It should be noted that this is probably a rare occurrence.

Storage conditions include any steps taken to protect the equipment, such as wrapping it in plastic film or nonwoven, or covering openings in the equipment with a bonnet of a plastic film or nonwoven. It also includes the room the equipment is stored in; conditions of the room include temperature, humidity, air quality, and external access.

How does one establish a maximum CEHT? It would be helpful to contact the manufacturing (or scheduling) group to find out, under normal conditions, what the longest time interval might be that the equipment would be unused after cleaning. The objective should be to adequately protect the equipment during that time period

(perhaps including a safety margin), and then to provide adequate justification that the equipment remains safe to use throughout that time period. One should analyze the storage situation (considering factors such as characteristics of the cleaned equipment, the nature of possible recontaminants, and the storage conditions), and see what can be done proactively to adequately protect the equipment from recontamination.

There are two main options for justifying the CEHT. One is professional judgment based on an analysis of the storage situation. For example, if the equipment is adequately cleaned and then stored dried, if all external ports or openings to the storage room atmosphere are closed or covered with a plastic film or nonwoven, and if the equipment is stored in a controlled room, one might just document that in a memo to justify a CEHT of several months. It should be noted that this approach has its limits; justifying a CEHT of one year by this method is probably unreasonable.

A second method of justifying the CEHT is to develop data. This would involve holding the cleaned equipment for the maximum CEHT, and then sampling surfaces and analyzing those samples for possible recontaminating residues. To do this, one must decide what the possible recontaminating species might be. As a general rule, these are limited to bioburden and "dust". Testing procedures for bioburden are relatively straightforward using accepted microbiological techniques. For "dust", one might consider either a particle counter, TOC, or perhaps even an enhanced visual inspection (a white or black cloth wipe). For sampling sites, one does not want to automatically sample the same sites that were sampled in the cleaning validation protocol; one must consider which sites are most likely to be recontaminated during storage. For example, for agitator blades, the bottom of the agitator blade (a worst-case cleaning location) may be the appropriate sampling point as part of the cleaning validation protocol; however, for determination of the CEHT, the top of the agitator blade may be the appropriate sampling point for "dust" (since the dust is more likely to settle on the top of the blades).

In addition to what to test for and where to sample, one must also set reasonable acceptance limits. In some cases, this is based on baseline data. For example, for bioburden one might specify an average increase of no more than one log in bioburden per contact plate or rinse sample. For "dust", certainly the expectation that the equipment be visually clean is appropriate. Beyond that, one might also specify a maximum change as being no more than double or triple the baseline determined by particle counting or by TOC estimates. This requires that one have a baseline measurement of the equipment at the end of cleaning.

This testing to determine a CEHT can be handled as part of the cleaning validation protocol, or could be handled as a separate test procedure. The amount of testing that is done to establish the CEHT will depend on how one handles it. If it is part of the cleaning validation protocol (either as part of the "normal" validation activities or a separate protocol), one should do three PQ runs. However, particularly if one has a reasonable justification for supporting a CEHT without data, and one wants only to confirm that judgment, then one might only perform one evaluation to support that professional judgment.

Issues that can complicate or simplify the CEHT involve any pre-rinse or sanitizing step that is utilized immediately prior to manufacture. If the potential recontaminating species is just "dust", this may be readily removed by a water pre-rinse. If the purpose of the pre-rinse is solely to reduce "dust" to an acceptable level, then that steps essentially becomes part of the cleaning process and must be validated. If a pre-rinse is done for other reasons, and has a side benefit of reducing extraneous "dust", then the pre-rinse may be used as another

part of the professional judgment as to why a separate study is not needed. For the initial sanitizing step, one must also consider any potential effects of residues of any non-volatile chemical sanitizers used.

If a CEHT is specified for a cleaning process, and if that CEHT is critical for control, then it is important to document that time. Documenting it means one needs to record the time of the end of the cleaning procedure and the time of the beginning of manufacture. The former should be defined based on one's cleaning process (but probably should not be based on a QC release time). The latter is defined based on one's manufacturing process. The important point here is that, if it is important to control the CEHT, then it needs to be measured in some way, and it should be defined.

A final issue to consider is what to do if the CEHT looks like it might be exceeded in an actual manufacturing situation. There are two options. Option 1 is to allow the CEHT to be exceeded, and then quarantine the equipment. The equipment is then tested in much the same manner as any initial testing to establish the CEHT. If it passes, it is released and there is some justification for extending the DEHT. In such a case, the released equipment should be used immediately. If it fails, it is cleaned and tested again. In that case, there is no justification for extending the CEHT. Option 2 is to clean the equipment (using the standard cleaning procedure) before the CEHT is exceeded. In this case one is merely cleaning (with a validated cleaning procedure) equipment that is already clean. In essence one is "re-setting" the CEHT. Which option is selected will depend on the relative costs and feasibility of each.

This Cleaning Memo is designed to present some basic information and to stimulate thought about the significance of the CEHT for validated pharmaceutical manufacturing. Application of these concepts should be based on both good scientific principles as well as what is practical and achievable in a given manufacturing environment.

Note: The acronym CEHT is not a standard abbreviation. It is used here solely so the words don't have to be written out each time.